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Clinical Pharmacokinetics and Administration of Established Platinum Drugs

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Abstract

We review the pharmacology and clinical administration of the commonly used platinum-based anticancer drugs cisplatin and carboplatin, and the more recently approved diamminocyclohexane-based oxaliplatin. The development of analogues of cisplatin has been focused upon identifying compounds with less toxicity and with a different spectrum of activity.

Carboplatin exemplifies the former, while the initial data with oxaliplatin support its activity in cisplatin-resistant tumours. The clinical pharmacokinetics of the drugs are reviewed. Incorporation of these data into the design of clinical regimens has permitted individualised therapy with carboplatin, and has enhanced safety. Additional investigation of the pharmacodynamics of all of these agents is expected to result in their selective application. The clinical effects of these analogues are discussed.

The early studies of the platinum-based antitumour drug cisplatin revealed it to be clinically challenging for patients and physicians alike. The initial human studies were characterised by severe nausea and vomiting, and nephrotoxicity in the form of renal failure almost led to studies being discontinued.[1] The demonstration by Cvitkovic and colleagues, first in an animal model, then in a clinical trial, that aggressive diuresis could prevent the severe renal damage permitted further development and investigation of the drug.[2,3] These methods are still in standard use today. Nausea and vomiting were ameliorated largely as a result of the investigation of intensive antiemetic regimens by Gralla and colleagues.[4] Ultimately, the discovery of serotonin (hydroxytryptamine; 5-HT_3) receptor blockers made this uncomfortable toxicity more manageable. The observation that patients with refractory tumours were deriving substantial benefit from treatment propelled continued clinical development.

In parallel with the continuing development of cisplatin, efforts were also directed towards finding alternative platinum compounds for clinical use. With the goals of diminishing toxicity and expanding the therapeutic spectrum, these resulted in the development of carboplatin and oxaliplatin, which, together with cisplatin, can be considered as the 'established' platinum drugs. This article provides a brief overview of the development of carboplatin and oxaliplatin, together with a comparison of clinical pharmacokinetics and practical clinical administration issues (including toxicity) for these drugs and for cisplatin.

1. Beyond Cisplatin: Development of Carboplatin and Oxaliplatin

The adverse effects of cisplatin prompted a parallel synthesis effort to design more effective and

less toxic analogues.[5] It was found that modification of cisplatin to contain less labile leaving groups alters both the pharmacokinetics and the toxicity profile of the drug. In a murine screen for nephrotoxicity, replacement of the chloride leaving groups with a cyclobutanodicarboxylato ligand, forming carboplatin (fig. 1), diminished renal effects, while antitumour activity was retained.[6] At effective doses, carboplatin produced substantially less nausea, vomiting, nephrotoxicity and neurotoxicity than cisplatin, and bone marrow suppression was its predominant toxicity.[7] Phase III trials have demonstrated the equivalence of carboplatin and cisplatin in the treatment of ovarian cancer,[8] but in testicular and head and neck cancers, cisplatin appears to be superior.[9,10] Therefore, on the basis of superior therapeutic index, together with greater ease of administration and more predictable individualised dosing (see sections 2 to 4), carboplatin has largely replaced cisplatin in the treatment of many but not all platinum-sensitive tumours.

Altering the structure of the leaving group influences tissue and intracellular distribution of the platinum coordination complex; however, the stable (carrier) amine group determines the structure of the adduct when bound to DNA. The adducts produced by cisplatin and carboplatin are largely identical, which explains their very similar patterns of tumour sensitivity. To find novel platinum agents with activity in cisplatin-resistant disease, a variety of carrier ligands were investigated.

Compounds containing the 1,2-diamminocyclohexane (DACH) ligand as a stable carrier group were first synthesised by Connors et al.,[5] and Burchenal et al.[11] first demonstrated their activity in murine models. Based on these studies (reviewed by Chaney[12]), a number of compounds were developed, but clinical application was limited by toxicity. However, Kidani synthesised oxaliplatin [DACH-oxalato platinum (II)], which has been successfully developed as an agent with activity in colorectal cancer.[13-15] Oxaliplatin adducts form more rapidly (15 minutes *vs* 12 hours) and are more toxic than those of cisplatin.[16,17] Oxaliplatin is active in several cisplatin-resistant tumour cell lines; moreover, comparative analysis of the results from the National Cancer Institute human tumour screen suggests that oxaliplatin and other DACH ligand-containing platinum drugs represent a distinct family of agents with a pattern of tumour sensitivity that differs from that of cisplatin.[18-20] The most important evidence supporting this concept is the activity of oxaliplatin in colorectal cancer, a disease in which cisplatin and carboplatin have no significant clinical activity.[21]

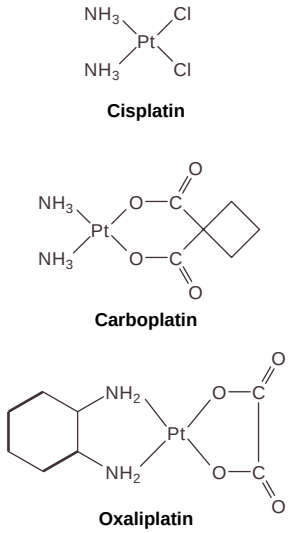

Fig. 1. Structures of platinum complexes.

2. Clinical Pharmacokinetics

This section provides a comparison of the pharmacokinetic properties of the 3 established platinum drugs cisplatin, carboplatin and oxaliplatin, together with a discussion of available data on pharmacokinetic-pharmacodynamic relationships.

2.1 Pharmacokinetics

As noted in section 1, the pharmacokinetic differences observed between platinum drugs may be attributed to the structure of their specific leaving

Table I. Comparative pharmacokinetics of platinum analogues following bolus or short intravenous infusion; data adapted from selected references

	Cisplatin	Carboplatin	Oxaliplatin	ZD0473
$t_{½\alpha}$ (min)				
Total platinum	14-49	12-98	26	
Ultrafiltrate	9-30	8-87	21	14
$t_{½\beta}$ (h)				
Total platinum	0.7-4.6	1.3-1.7		
Ultrafiltrate	0.7-0.8	1.7-5.9		2.0
$t_{½\gamma}$ (h)				
Total platinum	24-127	8.2-40	38-47	
Ultrafiltrate			24-27	76.3
Protein binding (%)	>90	24-50	85	
Urinary excretion (%)	23-50	54-82	>50	5-70

$t_{½\alpha}$, $t_{½\beta}$, $t_{½\gamma}$ = early, mid-, late half-lives.

groups. Platinum complexes containing leaving groups that are less easily displaced exhibit reduced plasma protein binding, longer plasma half-lives and higher rates of renal clearance. These features are evident in the pharmacokinetic properties of cisplatin, carboplatin and oxaliplatin, which are summarised in table I [data for the newer drug ZD0473, a sterically hindered platinum drug designed to prevent drug inactivation, are also included for comparative purposes, but are not discussed further in text (see the accompanying paper by Judson and Kelland for more details[22])]. Other aspects of platinum drug pharmacokinetics have been reviewed elsewhere.[23-25]

2.2 Cisplatin

After intravenous infusion, cisplatin rapidly diffuses into tissues and is highly bound to plasma protein.[26] Therefore, hydration schedules following cisplatin administration need not be protracted. The disappearance of ultrafilterable platinum is rapid and occurs in a biphasic fashion.[27,28] The bulk of cisplatin excretion is renal.[29,30]

2.3 Carboplatin

Pharmacokinetic differences observed between cisplatin and carboplatin (table I) depend primarily on the slower rate of conversion of carboplatin to a reactive species. Thus, the stability of carboplatin results in a low incidence of nephrotoxicity (see section 4.2). Carboplatin is also considerably less reactive with plasma proteins.[31] Plasma elimination of platinum following short intravenous infusions of carboplatin has been reported to occur in a biphasic or triphasic manner. The disappearance of ultrafilterable platinum is biphasic. Measures of total and ultrafilterable platinum yield similar values for the area under the plasma concentration-time curve (AUC), so total platinum provides a satisfactory estimate of drug exposure.

Carboplatin is excreted predominantly unmodified by the kidneys. The renal clearance of carboplatin is closely correlated with the glomerular filtration rate (GFR), which forms the basis of dosing strategies to individualise drug exposure.[32]

2.4 Oxaliplatin

Oxaliplatin has pharmacokinetic properties that are more similar to those of carboplatin than to those of cisplatin. After intravenous infusion, the drug is found in 3 identifiable compartments: plasma-bound platinum (oxaliplatin is highly protein bound[33]), ultrafilterable platinum and platinum associated with erythrocytes. Plasma elimination of total platinum and ultrafiltrate is biphasic.[25] Thus, as with carboplatin, there are no substantial differences between total and free drug kinetics. Like cisplatin, oxaliplatin appears to be retained in red blood cells longer than in plasma; it has been suggested that the red cell may act as a

reservoir of drug. However, unlike cisplatin, oxaliplatin does not accumulate to any significant extent following multiple courses of treatment.[33] This may explain why neurotoxicity associated with oxaliplatin is more rapidly reversible (see section 4.3). Oxaliplatin is eliminated predominantly by the kidneys.

2.5 Pharmacokinetic-Pharmacodynamic Relationships

Studies of pharmacokinetic-pharmacodynamic interactions attempt to relate indices of drug exposure to biological measures of drug effect (usually toxicity to normal tissues or killing of tumour cells). Two issues are addressed in such studies: can the effectiveness of the drug be enhanced, or the toxicity attenuated, by knowledge of its pharmacokinetics in an individual? These questions are appropriate to the use of cytotoxic agents with relatively narrow therapeutic indices.

Toxicity to normal tissues can be quantified as a continuous variable when the drug is myelosuppressive. Thus, the early studies of carboplatin demonstrated a close relationship of changes in platelet counts to the individual's AUC, which was itself closely related to renal function determined as creatinine clearance. On the basis of these observations, Egorin et al.[34] and Calvert et al.[35] derived formulas based on creatinine clearance to predict either the percentage change in platelet count or a target AUC. More recently, Chatelut and colleagues[36] derived a formula that relies on serum creatinine, as well as morphometric determinants of renal function.

Application of such pharmacodynamically guided dosing algorithms for carboplatin has been widely adopted as a means of avoiding overdosage and of maximising dose intensity in the individual. In an analysis by Jodrell et al.,[37] the likelihood of a tumour response (in patients with ovarian cancer) also increased with increasing AUC up to a level of 5 to 7 mg/ml · h but not at higher values. Similar results were obtained with carboplatin in combination with cyclophosphamide, and neither response rates nor survival were determined by the carboplatin AUC in patients with ovarian cancer.[38]

The relationship of pharmacokinetics to response may also be explored by investigating cellular pharmacology, i.e. the formation and repair of DNA adducts.[39] In patients with ovarian cancer treated with cisplatin-containing chemotherapy, responders had higher peak platinum-DNA adduct levels than nonresponders, although there was substantial overlap among the groups.[40] Schellens and colleagues[41] found that after cisplatin exposure, the peak DNA-adduct content in leucocytes and the area under the DNA adduct-time curve were important predictors of response, both individually and in logistic regression analysis, in patients with head and neck cancer. An adaptive dosing study in which the dose of cisplatin will be modified on the basis of DNA adduct levels is in progress.[42]

Based on the individual variability of pharmacokinetics and of genotypic determinants of tumour susceptibility, it seems most likely that direct investigations of these factors will assist in determining how best to use platinum compounds. Characterisation of single nucleotide polymorphisms associated with toxicity, and tumour gene expression profiles determining susceptibility, will, it is hoped, allow further enhancement of the therapeutic index by allowing prospective identification of sensitive and resistant populations.

3. Formulation and Administration

3.1 Cisplatin

Cisplatin is administered intravenously over 0.5 to 2 hours as a chloride-containing solution. To minimise the risk of nephrotoxicity, patients are prehydrated with at least 500ml of salt-containing fluid. Immediately before cisplatin administration, mannitol (12.5 to 25g) is given parenterally to maximise urine flow. A diuretic such as furosemide may be used. All patients must receive parenteral antiemetics, usually dexamethasone with a 5-HT_3 antagonist.

A minimum of 1L of posthydration fluid is usually given after cisplatin administration.[1] The intensity of hydration varies somewhat with the dose of cisplatin.

High dose cisplatin (up to 200 mg/m^2 per course) may be administered in a formulation containing 3% sodium chloride, but such a high dose is rarely used.

Cisplatin may also be administered regionally to increase local drug exposure and diminish adverse effects. Its intraperitoneal use was first described by Ozols et al.[43] and Howell et al.[44] Drug exposure in the peritoneal cavity is some 50-fold higher than that achieved with intravenous administration.[44] Data from a randomised parallel-group trial in ovarian cancer patients with low volume disease suggest that, at standard doses, intraperitoneal administration is superior to intravenous cisplatin in combination with intravenous cyclophosphamide.[45] The development of combinations of carboplatin with paclitaxel has, however, superseded this technique in ovarian cancer, and the intraperitoneal route is now infrequently used. Regional use also includes intra-arterial delivery (as for hepatic tumours, melanoma and glioblastoma), but this has not been adopted as a standard method of treatment.

There is growing interest in chemo-embolisation for the treatment of tumours confined to the liver, and cisplatin is a common component of regimens used in this setting.[46]

3.2 Carboplatin

Cisplatin treatment requires significant clinical resources and is tiring for patients. Although previously given as in-hospital treatment, it is now usually administered in the outpatient setting. The demands of the modern healthcare environment have contributed to the expanding use of carboplatin as an alternative to cisplatin except in circumstances where cisplatin is clearly the superior agent.

Carboplatin is substantially simpler to administer than cisplatin. Extensive hydration is not required because of the lack of nephrotoxicity at standard doses.[47] Carboplatin is reconstituted in chloride-free solutions (unlike cisplatin, since chloride can displace the leaving groups) and administered over 30 minutes as a rapid intravenous infusion. It has been incorporated in high dose chemotherapy regimens at doses over 3-fold higher than those of the standard regimens.[48] In some regimens, continuous infusion has been substituted for a rapid intravenous infusion. It is doubtful that there is an advantage for this approach.

3.3 Oxaliplatin

Oxaliplatin is also uncomplicated in its clinical administration. For bolus administration of oxaliplatin, the required dose is administered in 500ml of chloride-free diluent as a 2-hour infusion. In studies in colorectal cancer, oxaliplatin has been administered as a 5-day continuous infusion, during which the dosage rate has been modified to observe principles of chronopharmacological administration.[49] Oxaliplatin is more frequently given as a single dose every 2 weeks (85 mg/m^2) or every 3 weeks (130 mg/m^2), alone or with other active agents. It is usual to pretreat patients with active antiemetics, such as a 5-HT$_3$ antagonist, but nausea is not as severe as with cisplatin (see section 4.3). No prehydration is required. The predominant toxicity of oxaliplatin is neurotoxicity (see section 4.3): the development of an oropharyngeal dysaesthesia, often precipitated by exposure to cold, requires prolonging the duration of administration to 6 hours.

4. Toxicity

A substantial body of literature documents the adverse effects of platinum compounds. Table II lists the predominant toxicities of cisplatin, carboplatin and oxaliplatin; toxicity information for the newer platinum compounds ZD0473 and BBR3464 is also included for comparative purposes, but is not discussed further here (see the accompanying paper by Judson and Kelland[22]). The nephrotoxicity of cisplatin almost led to abandonment of the clinical development of this

Table II. Toxicity profiles of platinum analogues currently in clinical use

	Cisplatin	Carboplatin	Oxaliplatin	ZD0473	BBR3464
Myelosuppression		•		•	•
Nephrotoxicity	•				
Neurotoxicity	•		•		
Ototoxicity	•				
Diarrhoea					•
Nausea/vomiting	•	•	•	•	•

drug, until Cvitkovic and colleagues introduced aggressive hydration, which prevented the development of acute renal failure.[2,3] As noted earlier, the toxicity of cisplatin was a driving force in the search both for less toxic analogues and for more effective means of managing its adverse effects, especially nausea and vomiting.

4.1 Cisplatin

The principal adverse effects associated with cisplatin (at single doses ≥50 mg/m^2) include nausea and vomiting, nephrotoxicity, ototoxicity, neuropathy and occasionally myelosuppression. Rare effects include visual impairment, seizures, arrhythmias, acute ischaemic vascular events, glucose intolerance and pancreatitis.[1] The current state-of-the-art treatment for nausea and vomiting is a 5-HT$_3$ antagonist plus a glucocorticoid steroid,[4] although other combinations of agents are still widely used. In the weeks after treatment, continuous antiemetic therapy may be required. Nephrotoxicity is ameliorated but not completely prevented by hydration. Renal damage, to both glomeruli and tubules, is cumulative, and serum creatinine level is not a reliable guide to GFR after cisplatin treatment. Acute elevation of serum creatinine levels may occur after a cisplatin dose, but levels return to normal with time. Tubule damage may be reflected in a salt-losing syndrome that resolves with time.

Ototoxicity is a cumulative and irreversible adverse effect of cisplatin treatment resulting from damage to the inner ear. Therefore, audiograms are recommended every 2 to 3 cycles.[1] The initial audiographic manifestation is loss of high frequency acuity (4000 to 8000Hz). When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Peripheral neuropathy is also cumulative, although less common than with agents such as vinca alkaloids. This neuropathy is usually reversible, although recovery is often slow. A number of agents with the potential for protection from neuropathy have been developed, but none is yet used widely.[50]

4.2 Carboplatin

Myelosuppression, which is not usually severe with cisplatin, is the dose-limiting toxicity of carboplatin.[47] The drug is most toxic to the platelet precursors, but neutropenia and anaemia are frequently observed. The lowest platelet counts are observed 17 to 21 days after a single dose of carboplatin, and recovery usually occurs by day 28. The effect is dose dependent, but individuals vary widely in their susceptibility. As shown by Egorin et al.[34] and Calvert et al.,[35] the severity of platelet toxicity is strongly correlated with AUC. Both groups derived pharmacologically based formulas to predict toxicity and guide carboplatin dosing. That of Calvert and colleagues[35] targets a particular exposure to carboplatin:

$$\text{Dose (mg)} = \text{Target AUC (mg/ml} \cdot \text{min)} \times [\text{GFR (ml/min)} + 25]$$

This formula has been widely used to individualise carboplatin dosing and permits targeting to an acceptable level of toxicity.

Although patients who are elderly or those with poor performance status or a history of extensive pretreatment have a higher risk of toxicity even when dose is calculated using the available formulae,[34,35] the overall safety of drug administration has been enhanced. For the combination of carboplatin and paclitaxel, AUC-based dosing has

helped to maximise the dose intensity of carboplatin.[51] Doses some 30% higher than those resulting from a strategy based solely on body surface area have been used safely. Determination of whether this approach to dosing improves outcome requires a randomised trial, and such a trial is in progress.

The other toxicities of carboplatin are generally milder and better tolerated than those of cisplatin. Nausea and vomiting, though frequent, are less severe, shorter in duration, and more easily controlled with standard antiemetics (for example prochlorperazine, dexamethasone, lorazepam) than following cisplatin treatment. Renal impairment is infrequent. Alopecia is common, especially with the paclitaxel-containing combinations. Neurotoxicity is also less common than with cisplatin, although it is observed more frequently with the increasing use of high dose regimens. Ototoxicity is also less common than with cisplatin. As might be expected, the incidence of neurological effects appears to be cumulative, and patients receiving higher doses should be carefully monitored.

4.3 Oxaliplatin

The dose-limiting toxicity of oxaliplatin is sensory neuropathy, a characteristic of all DACH-containing platinum derivatives. The severity of the toxicity is dramatically less than that observed with another DACH-containing analogue, ormaplatin. Oxaliplatin-induced sensory neuropathy takes 2 forms. The first is a tingling of the extremities, which may also involve the perioral region, and occurs early in treatment and usually resolves within a few days. With repeated dosing, symptoms may last longer between cycles, but do not appear to be of long duration or cumulative. Laryngopharyngeal spasm and cold dysaesthesias have also been reported, but are not associated with significant respiratory symptoms and can be prevented by prolonging the duration of infusion. A second neuropathy, more typical of that seen with cisplatin, affects the extremities and increases with repeated doses.

The neurological effects of oxaliplatin appear to be cumulative in that they become more pronounced and of greater duration with successive cycles; however, unlike those of cisplatin, they are rapidly reversible with drug cessation. In a review of 682 patient experiences, Brienza et al.[52] reported that symptoms regressed within 4 to 6 months of treatment in 82% of patients who experienced neurotoxicity at grade 2 or above. Definitive physiological characterisation of oxaliplatin-induced neuropathy has proven difficult in large studies. Extra and colleagues[53] reported that electromyograms performed in 6 oxaliplatin-treated patients revealed an axonal sensory neuropathy, but nerve conduction velocities were unchanged. Peripheral nerve biopsies performed in the same study showed decreased myelinisation and replacement with collagen pockets.

Oxaliplatin has not been associated with nephrotoxicity or ototoxicity. Nausea and vomiting do occur and generally respond to 5-HT_3 antagonists. Myelosuppression is uncommon and is not severe with oxaliplatin as a single agent, but is a feature of combination regimens involving this drug.

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